REMARKS

Claims 26, 28-31, and 33-42 are pending in the application. Claims 24, 25, and 35-39 are withdrawn as being drawn to non-elected inventions. Claims 26-34 are under active consideration. Claims 24, 25, 27, and 32 have been canceled, claims 26, 28, 29, 31, 33, and 34 have been amended, and new claims 40-42 have been added. Claims 26, 29, 33, and 34 have been amended to further clarify the intended subject matter of the claimed invention and to address the rejections under 35 U.S.C. § 112, first and second paragraphs. Claim 29 has been amended to recite "a recombinant polynucleotide comprising a vector and a polynucleotide of claim 26" to address the written description rejection under 35 U.S.C. § 112, first paragraph. Support for this amendment to claim 29 can be found in the specification, for example, at page 2, lines 23-25 and page 13. Claim 30 c) and d) have been amended to recite polynucleotides that are "completely complementary" to address the rejection under 35 U.S.C. § 112, second paragraph. Support for this amendment to claim 30 can be found in the specification, for example, at page 5, lines 22-24. Claims 26 and 31 have been amended and new claims 40-42 have been added to address the rejection under 35 U.S.C. § 112, second paragraph, particularly with regard to the Examiner's concern that the term "immunogenic fragment" cannot properly be referred to as a polypeptide because "the conventional meaning of a 'polypeptide' does not include such short sequences" (Office Action, page 11). Support for the new claims can be found in the specification, for example, at page 2, lines 15-25 and page 7, lines 4-5. No new matter is added by these amendments or new claims. Entry of these amendments are respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Objections to the Specification

The Examiner objected to the presence of references to hyperlinks and/or other forms of browser-executable code in the specification (Office Action, page 3). Applicants did not intend to have active links in the specification, nor to incorporate the subject matter of websites by reference to such hyperlinks. Applicants have amended the specification to remove active hyperlinks and therefore respectfully request that the Examiner withdraw the objection to the specification.

The Examiner objected to the amendment filed May 10, 2003 on the grounds that the material added to the paragraph starting at page 9, line 33 is allegedly "not supported by the original disclosure" (Office Action, page 3). As the Examiner correctly notes, the table compares three nucleotide sequences to that of SEQ ID NO:2. Accordingly, the table has been amended to specify the nucleotide sequence of SEQ ID NO:2 in column 1 rather than the amino acid sequence of SEQ ID NO:1 to correct this obvious and unintentional error. Applicants have also amended the second sentence of the paragraph at page 9, lines 28-29 as follows: "These preferred variants have about 90% identity to ~~the human protein~~ SEQ ID NO:2 as shown in the table below." The Examiner states that a "sequence search performed at USPTO does not reveal said percent identity for SEQ ID NO:1 or for the encoding sequence of SEQ ID NO:2 when aligned with any sequence in the Sequence Listing" (Office Action, pages 3-4). Applicants disagree, and direct the attention of the Examiner to Exhibit A, which shows the results of a Blast analysis comparing the sequence of SEQ ID NO:2 to each of the sequences specified in the table. The three sequences do show the indicated percentage identities over the residue ranges specified in column 5 of the table. Applicants also amended column 2 of the table to correct inadvertent errors in the listing of SEQ ID NOs. The clone 008031_Cf.1 encompasses SEQ ID NO:9, but does not correspond to any sequence in the Sequence Listing, hence the SEQ ID NO has been deleted from column 2 for that sequence. The clone 034237_Mm.1 clearly corresponds to SEQ ID NO:10 as shown on page 6 of the Sequence Listing. The clone 702482342 clearly corresponds to SEQ ID NO:11 as shown on page 7 of the Sequence Listing. The corrections to the SEQ ID NOs in column 2 are necessary in order to make them correctly correspond to the Sequence listing, and Applicants respectfully request that the Examiner enter this amendment. Withdrawal of the objection to the specification is respectfully requested.

Rejoinder of Claims

The Examiner is reminded that claims 35-39, drawn to methods of using the elected polynucleotides of Group I, should be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of any product claim, for rejoinder of process claims covering the same scope of

products. Applicants request that claims 35-39 be rejoined and examined upon allowance of any claim drawn to the polynucleotides of Group I.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 26 and 29-34 have been rejected under the first paragraph of 35 U.S.C. 112 for allegedly introducing new matter into the specification. Applicants traverse the rejection for the reasons already made of record in the response to the Office Action of March 14, 2003 and on the following grounds.

Claim 26 b) and claim 33 b) have been canceled; therefore, the rejection with respect to these claims is moot.

For at least these reasons, withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejections under 35 U.S.C. § 101 and § 112

Claims 26-34 are rejected under 35 U.S.C. § 101 and § 112 because the claimed invention is allegedly "not supported by either a specific and substantial asserted utility or a well established utility," and one skilled in the art, therefore, would not know how to use the claimed invention (Office Action, page 5). Applicants traverse the rejections for the reasons already made of record in the responses to the Office Actions of September 12, 2002 and March 14, 2003, the Declaration of Dr. Tod Bedilion, the Brief on Appeal, and on the following grounds.

I. The rejection of claims 26-34 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

To further address the rejections under 35 U.S.C. § 101 and § 112, Applicants submit three additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references filed before or shortly after the September 23, 1997 priority date of the instant application.

The instant application is a continuation-in-part application of and claims priority to United States patent application Serial No. 08/933,750 (hereinafter "the Lal '750 application")

filed on September 23, 1997. The SEQ ID NO:1-encoding polynucleotides were described in the Lal '750 application.

The First Bedilion Declaration, Rockett Declaration, Iyer Declaration, Second Bedilion Declaration, and the ten (10) references fully establish that, prior to the September 23, 1997 filing date of the parent Tang '808 application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;
>
> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;
>
> nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;
>
> accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;
>
> biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

> the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;
>
> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;
>
> failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and
>
> failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

As demonstrated by the First Bedilion Declaration, the Rockett Declaration, the Iyer Declaration, and the Second Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise biological function.

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1998 would have understood that any expressed polynucleotide is useful for a number of gene expression monitoring applications, *e.g.*, in cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s . . . that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology.[1] (Rockett Declaration, ¶ 18.)

In his second Declaration, Dr. Bedilion explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression

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"Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

monitoring applications using cDNA microarrays. (Second Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include and as a biologist I would want my microarray to include each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

In addition, Dr. Rockett explains in his Declaration that "there are a number of other differential expression analysis technologies that precede the development of microarrays, some by decades, and that have been applied to drug metabolism and toxicology research, including: (1) differential screening; (2) subtractive hybridization, including variants such as chemical cross-linking subtraction, suppression-PCR subtractive hybridization and representational difference analysis; (3) differential display; (4) restriction endonuclease facilitated analyses, including serial analysis of gene expression (SAGE) and gene expression fingerprinting and (5) EST analysis." (Rockett Declaration, ¶ 7.)

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, e.g., as described by Bedilion, Rockett, and Iyer in their Declarations.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett Declaration, Exhibit C, page 656)

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7).

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]
>
> The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]
>
> The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]
>
> Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof." [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

> Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]
>
> Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Appellants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> The invention provides a "method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens." [abstract]
>
> "[W]e see each individual gene product as a 'pixel' of information which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,'in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood." [page 2]
>
> "The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given

biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts." [page 6]

"High resolution analysis of gene expression be used directly as a diagnostic profile. . . . " [page 7]

"The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed." [page 7]

"The invention . . . includes a method of comparing specimens containing gene transcripts." [page 7]

"The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens." [i.e., the results yield analogous data to microarrays] [page 8]

"Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made." [page 8]

"In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities." [page 9]

"In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . " [page 9]

"[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells." [pages 9 10]

"The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as 'gene transcript image analysis' or 'gene transcript frequency analysis'. The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism." [page 11]

"The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few." [page 12]

"[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates." [page 12]

"For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . ." [page 12]

"In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . " [page 12]

"In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond." [page 12]

"In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models." [page 14]

"In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition." [page 14]

"An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined." [page 15]

"[T]his research tool provides a way to get new drugs to the public faster and more economically." [page 36]

"In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker." [page 38]

"[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation

with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients." [page 39]

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 1995, describes an expression profiling platform, the "genome reporter matrix", which is different from nucleic acid microarrays. Additionally describing use of nucleic acid microarrays, the 588 patent makes clear that the utility of comparing multidimensional expression datasets is independent of the methods by which such profiles are obtained. The 588 patent speaks clearly to the usefulness of such expression analyses in drug development and toxicology, particularly pointing out that a gene's failure to change in expression level is a useful result. Thus, with emphasis added,

> The invention provides "[m]ethods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug." [abstract]
>
> "The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism." [col. 1]
>
> "The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix." [col. 2]
>
> "Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects." [cols. 2 - 3]

"Furthermore, it is not necessary to know the identity of any of the responding genes." [col. 3]

"[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical." [col. 4]

"The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters." [col. 4]

" A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included." [cols. 6 7]

"In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug." [cols. 7 8]

"In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization

pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile." [col. 8]

"The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses." [col. 8]

"Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli." [col. 9]

"The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s)." [col. 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (reference "h" attached hereto), and the September 15, 1997 news report by Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," *Genetic Engineering News* (reference "i" attached hereto), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), published April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the reference describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

"[T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates." [Field of the invention]

"An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems." [page 3]

"Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals." [page 3]

"The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity." [page 3]

"As used herein, the terms 'gene expression profile,' and 'gene expression pattern' which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand." [page 7]

"The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . " [page 7]

Therefore, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

II. Applicants' Showing of Facts Overcomes The Examiner's Concern That Applicants' Invention Lacks "Specific Utility"

The Examiner alleges that the asserted utility for the claimed polynucleotides is not specific (Office Action, page 5).

Appellants' submission of additional facts overcomes this concern. Those facts demonstrate that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Appellants' claimed polynucleotides as gene-specific probes ***depends upon*** specific properties of the polynucleotides, that is, their nucleic acid sequences.

"[E]ach probe on . . . [a "high density spotted microarray[]"], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, ***binds specifically*** and with minimal cross-hybridization, to the probe's cognate transcript"[1]; "[e]ach gene included as a probe on a microarray provides ***a signal that is specific to the cognate transcript***, at least to a first approximation."[2] Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene expression profiling"[3]; equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectable by the device, increasing the resolving power of the device."[4]

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established

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1 Declaration of Dr. John C. Rockett, ¶ 10(i), emphasis added.

2 Declaration of Dr. Vishwanath R. Iyer, ¶ 7 (emphasis added). See the footnote at ¶ 7 for a slightly more "nuanced" view.

3 Declaration of Dr. John C. Rockett, ¶ 10(ii).

4 Declaration of Dr. Vishwanath R. Iyer, ¶ 7.

underpinning of many, perhaps most, molecular biological techniques developed over the past 30 - 40 years.

For at least the above reasons, withdrawal of the rejection under 35 U.S.C. § 101 is respectfully requested.

III. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

Written description Rejection under 35 U.S.C. § 112, first paragraph

Claims 26, 29-31, 33, and 34 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of adequate written description. This rejection is traversed on the following grounds.

In particular, the Examiner alleges that there is not adequate support in the specification for "a DNA encoding a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:1 or a naturally occurring DNA that is at least 90% identical to SEQ ID NO:2" (Office Action, pages 4-5). Claims 26 b) and 33 b) have been canceled; therefore, the rejection with respect to these claims is moot.

The Examiner also alleges that there is no support for the claim language "a promoter sequence operably linked to a polynucleotide" as recited in claim 29. Although not conceding to the propriety of the rejection, in order to expedite prosecution, Applicants have amended claim 29 to recite "a recombinant polynucleotide comprising a vector and a polynucleotide of claim 26." Support for this amendment to claim 29 can be found in the specification, for example, at page 2, lines 23-25 and page 13. Therefore, no new matter is added by the current amendment.

For at least the above reasons, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 31 and 33 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite (Office Action, page 11). In particular, it is asserted that in claim 31, the term polypeptide is "confusing" because claim 31 c) is drawn to a method of producing a polypeptide wherein said polypeptide is an immunogenic fragment and allegedly "[t]he conventional meaning of a 'polypeptide' does not include such short sequences." In claim 33, the term "complementary" is allegedly indefinite because "the specification teaches that 'degree of complementarity and the use of nucleotide analogs affect the efficiency and stringency of hybridization reactions" and therefore "it is impossible to know the metes and bounds of the claim" (Office Action, page 12).

To expedite prosecution, claim 31 has been amended to remove part c), which recited an immunogenic fragment. Claim 26 c), though not specifically mentioned in the rejection, has been similarly amended. New claims 40-42, drawn to polynucleotides encoding an immunogenic portion of a polypeptide having the sequence of SEQ ID NO:1, recombinant polynucleotides encoding immunogenic portions, and a method of producing an immunogenic portion, respectively, have been added to replace the immunogenic fragment embodiments of claims 26 and 31.

To expedite prosecution, claim 33 c) and d) have also been amended as suggested by the Examiner to recite that the claimed polynucleotides are **completely** complementary.

These amendments further clarify the intended subject matter of the claimed invention. For at least the above reasons, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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Enclosures:

1) Declaration of John C. Rockett, Ph.D., under 37 C.F.R. §1.132, with Exhibits A - Q;

2) Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132;

3) Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A - E; and

4) ten (10) references published before the filing date of the instant application:

a) WO 95/21944, SmithKline Beecham, "Differentially expressed genes in healthy and diseased subjects" (Aug. 17, 1995)

b) WO 95/20681, Incyte Pharmaceuticals, "Comparative Gene Transcript Analysis" (Aug 3, 1995)

c) Schena et al., "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray," Science 270:467-470 (Oct 20, 1995)

d) WO 95/35505, Stanford University, "Method and apparatus for fabricating microarrays of biological samples" (Dec 28, 1995)

e) U.S. Pat. No. 5,569,588, Ashby et al., "Methods for Drug Screening" (Oct 29, 1996)

f) Heller al., "Discovery and analysis of inflammatory disease-related genes using cDNA microarrays," *PNAS* 94:2150 - 2155 (Mar 1997)

g) WO 97/13877, Lynx Therapeutics, "Measurement of Gene Expression Profiles in Toxicity Determinations" (April 17, 1997)

h) Acacia Biosciences Press Release (August 11, 1997)

i) Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," Genetic Engineering News (Sept. 15, 1997)

j) DeRisi *et al.,* "Exploring the metabolic and genetic control of gene expression on a genomic scale," Science 278:680 - 686 (Oct 24, 1997)

5) Exhibit A